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Kinetic Analysis of Recurrence and Survival After Potentially Curative Resection of Nonsmall Cell Lung Cancer

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Background: About two-thirds of the patients with nonsmall cell lung cancer (NSCLC) who undergo a potentially curative resection eventually suffer from recurrent disease. However, it has yet to be elucidated as to how survival after recurrence is influenced by different variables, including timing, type of recurrence, or other clinicopathological features. There have been few studies concentrating on the kinetics of growth of occult micrometastatic tumor cells that eventually manifest as tumor recurrence.
Methods: We retrospectively reviewed the charts of 197 patients who developed recurrence after a potentially curative resection for NSCLC.
Results: The median disease-free interval was a little over 1 year (395 days), as was the median postrecurrence survival—383 days. We created a model for the kinetics of recurrence by assuming that: (1) a tumor of 10^9 cells is the usual limit of detection, (2) patients generally die before the tumor reaches 10^{12} cells, and (3) it takes 1 year for average lung cancer cells to show a 10-fold increase. The model indicated that as much as 10^9 tumor cells should have been present immediately after the operation. Alternatively, the residual tumor cells should have an accelerated growth after the surgery.
Conclusions: These models indicate the importance of developing a sensitive detection method for occult metastatic cells and to understand the tumor dormancy mechanism.

KEY WORDS: **disease-free interval, postrecurrence survival, occult metastasis, tumor dormancy, multivariate analysis**

INTRODUCTION

Surgery offers the best chance for a cure of nonsmall cell lung cancer (NSCLC), although the disease is too advanced for operation at the time of presentation in 70% of those patients [1]. Furthermore, about two-thirds of the patients who undergo a potentially curative resection eventually suffer from recurrent disease [1]. Previous studies have shown that initial distant metastasis is more common than local recurrence, which indicates the need for systemic perioperative adjuvant therapy [2].

It is known that most instances of treatment failure occur within the first 3 years after resection and most deaths occur during the first 12–24 months [3,4]. However, it has yet to be elucidated as to how survival after recurrence is influenced by different variables, including timing, type of recurrence, or other clinicopathological features. There have been few studies concentrating on the kinetics of growth of occult micrometastatic tumor cells that eventually manifest as tumor recurrence.

In this study, we retrospectively studied 197 patients who suffered from tumor recurrence after a potentially curative resection for NSCLC. We analyzed the data, paying special attention to the kinetics of recurrence and

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postrecurrence survival, while trying to create a model of recurrence after pulmonary resection.

MATERIALS AND METHODS

Patients

During the 15-year period from 1980–1994, we performed 544 potentially curative pulmonary resections to treat NSCLC. We reviewed the charts of 197 cases in which clinical recurrence was detected in the follow-up period and whose data regarding the recurrence pattern and time were well documented. There were 135 men and 62 women, with ages ranging from 23 to 83 years (median 65), including 63 cases of squamous cell carcinoma, 119 adenocarcinomas, 9 large cell carcinomas, and 6 others. The last three groups were collectively referred to as nonsquamous cell carcinoma in the subsequent analyses. Ninety patients had stage I disease, 30 stage II disease, 71 stage IIIa disease, and 6 had stage IIIb disease.

Either a lobectomy or pneumonectomy with a formal ipsilateral mediastinal lymph node dissection was performed on 181 patients (92%), whereas such operations without lymph node dissection were performed in 12 patients and a wedge resection of the lung was performed in four patients, mainly due to a poor cardiopulmonary reserve. Postoperative staging was done in conjunction with the mapping of regional lymph node metastases and the determination of histologic type, tumor size, visceral pleural involvement, and clearance at the bronchial resection margins.

The patients were subsequently followed up at our outpatient clinic monthly for the first year, bimonthly during the second year, at 3-month intervals during the third year, at 4-month intervals during the fourth year, and twice a year thereafter. The evaluation included a physical examination, chest X-ray, and a tumor marker determination at every visit. If the patients demonstrated any signs or symptoms of recurrence, they received a further evaluation. In the apparently healthy patients, a chest and upper abdominal CT scanning and bone scintigram were performed at least once a year.

We defined *locoregional recurrence* as evidence of the disease at the bronchial stump, at the regional lymph nodes, or the presence of malignant pleural effusion, and *distant recurrence* as disease that had spread via the bloodstream, e.g., metastases to the brain, lung, bone, liver, etc.

Statistical Analysis

For a comparison of the proportions, the χ^2 test was used. The Kaplan-Meier method was used to estimate the probability of survival as a function of time [5], and survival differences were analyzed by the log-rank test [6]. The Cox proportional hazards modeling technique was used to identify which independent factors had a jointly significant influence on survival [7].

TABLE I. Nonsmall Cell Lung Cancer: Type of Recurrence

Type	No. cases
Distant metastases	138 (squamous 34, nonsquamous 104) (stage I 71, II 18, IIIa 47, IIIb 2) lung 53, brain 34, bone 25, skin 5, adrenal 4, liver 4, multiple sites 13
Locoregional recurrence	47 (squamous 25, nonsquamous 22) (stage I 17, II 9, IIIa 17, IIIb 4) lymph node 32 (hilar 1, mediastinum 20, neck 11) bronchial stump 12 pleural dissemination 3
Multiple recurrence (distant plus locoregional)	12 (squamous 4, nonsquamous 8) (stage I 2, II 3, IIIa 7, IIIb 0)

RESULTS

Type of Recurrence

The sites of the first failure are listed in Table I. In 138 cases (70%), the first site of recurrence was distant metastases. Metastases to the lungs, brain, and bone were the three most frequent sites of distant failure and were found in 53, 34, and 25 cases, respectively. Forty-seven patients (24%) suffered from locoregional recurrence. In 32 patients, the first site of the recurrence was the regional lymph nodes. Pleural dissemination was the site of the first failure in three cases, and 12 cases recurred as a tumor arising from a bronchial stump. Twelve patients were found to have both distant metastases and locoregional lesions as the site of initial failure. In squamous cell carcinoma, 34/63 (54%) of the patients had distant metastases as the first failure, whereas in adenocarcinoma 104/134 (75%) of the patients did so, and this difference was statistically significant ($P = 0.0002$).

Disease-free Interval (DFI)

The distributions of DFI (i.e., time from the operation to detection of the recurrence) with respect to various clinical features are shown in Figure 1. The median DFI was 395 days and in 75% of the cases recurrence occurred by 729 days. Based on a univariate analysis using the log rank test, factors that shortened the DFI were squamous cell carcinoma ($P = 0.0288$) and advanced stage ($P = 0.0046$) (Fig. 1C,D). The DFI tended to be shorter in patients with a locoregional recurrence (median DFI, 314 days) than in those with a distant recurrence (median DFI, 454 days) ($P = 0.0673$) (Fig. 1B, Table II). However, Cox's proportional hazards model indicated that the disease stage was the only independent variable contributing to a shortened DFI (Table III, model 1).

Survival After Disease Recurrence

From a clinically practical point of view, it is important to predict how long patients will survive from the day of

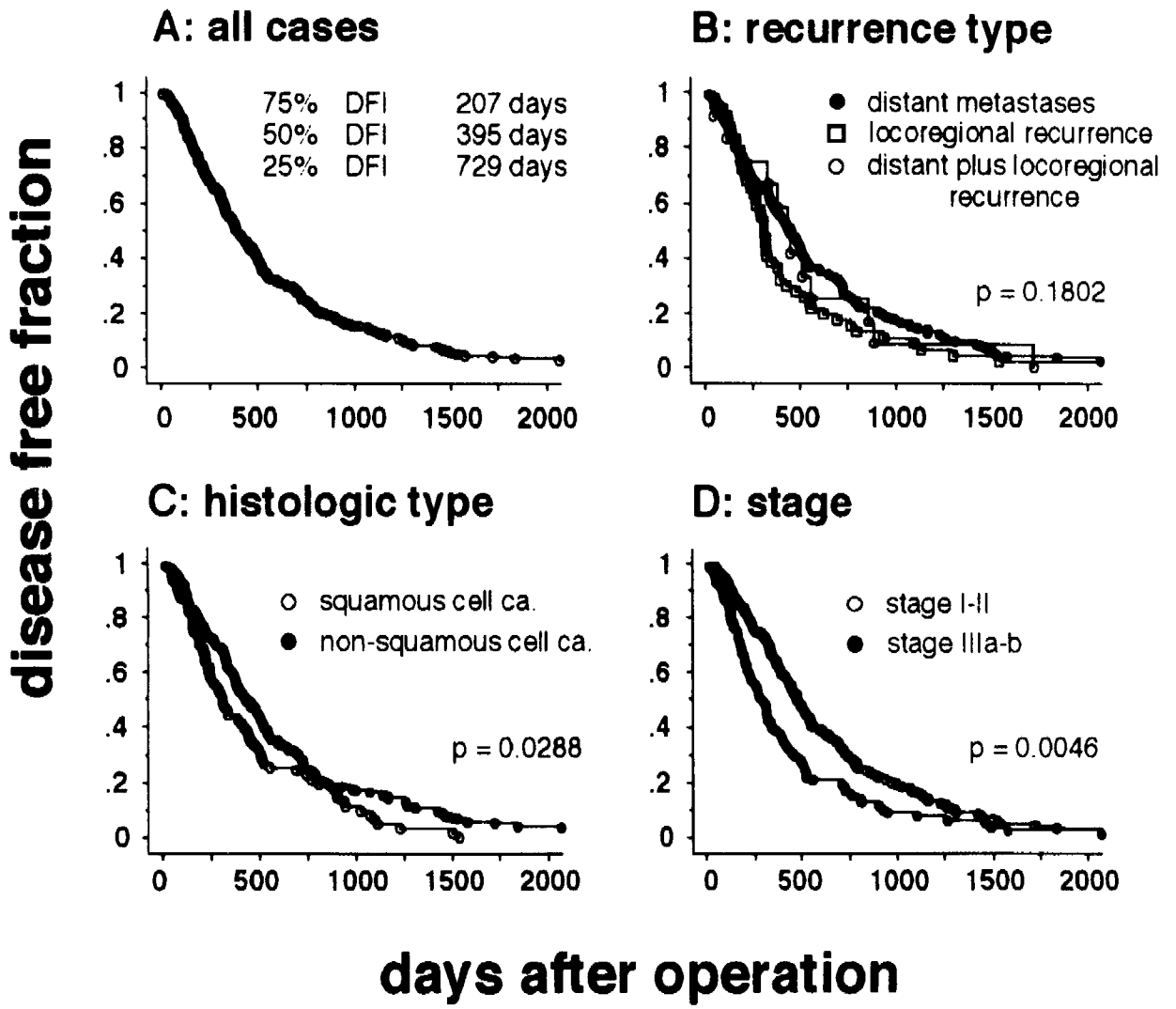

Fig. 1. Effects of various factors on the kinetics of recurrence.

recurrence detection. Figure 2 shows the postrecurrence survival curves by various clinical variables. The median survival was 383 days, and 75% of the patients died by 756 days after detection of the recurrence. A short DFI (1 year or less), advanced disease, and male gender were variables that significantly shortened the postrecurrence survival according to the log rank test (Fig. 2C,D). The type of the recurrence did not affect the postrecurrence survival in general (Fig. 2E). However, when an analysis was performed with respect to the metastasized organs, patients with brain metastases had the shortest survival (median, 204 days) followed by those with bronchial stump recurrence (median, 266 days), whereas patients with pulmonary metastases had a relatively long post-recurrence survival (median, 645 days) (Table II). In a multivariate analysis using Cox's proportional hazards model, male gender and short DFI were two independent predictors for a shortened postrecurrence survival (Table III, model 2).

Kinetic Model for Tumor Recurrence After Pulmonary Resection

The minimum detectable body burden of tumors in humans is generally between 10^9 (1 g) and 10^{10} cells, and patient death occurs when the tumor cell number reaches a level between 10^{11} and 10^{12} or 1 kg [8–10]. The doubling time of lung cancer cells as measured by at least two serial chest Xrays is reported to range from 30 days to 490 days, with a median of 120 days [11,12]. An average lung cancer with a doubling time of 100 days takes 332 days, or slightly less than 1 year, to have a 10-fold increase in volume, because $2^{3.32} = 10$. In this study, average tumor diameter was 42 mm, and thus average volume was 37 cm^3, which thus contained 3.7×10^{10} cells at the time

TABLE II. Relationship Among Site of First Failure and Disease-free Interval, Postrecurrence Survival, and Overall Survival in Nonsmall Cell Lung Cancers

Site of first failure	n	Median DFI[a] (days)	Median postrecurrence survival (days)	Median survival after operation (days)
Lung	53	523	645	1,284
Brain	34	436	204	776
Bone	25	395	390	1,032
Lymph node	32	314	364	830
Bronchial stump	12	235	266	545
All cases	197	395	383	897

[a]Disease-free interval.

TABLE III. Cox's Proportional Hazards Model for Factors Associated With Survival of Patients With Nonsmall Cell Lung Cancer

Model	Variable	Category	*P*	Hazards ratio[a]	95% confidence interval[b]
1[c]	Sex	male		1	
		female	.7974	.9600	.704–1.310
	Histology	nonsquamous		1	
		squamous	.1030	1.309	.947–1.809
	Stage	IIIa–b		1	
		I–II	.0038	.651	.486–.870
	Recurrence type	locoregional		1	
		distant	.1504	.770	.540–1.099
		locoregional plus distant	.5747	.831	.436–1.586
2[d]	Sex	male		1	
		female	.0090	.612	.424–.885
	Histology	nonsquamous		1	
		squamous	.9130	1.021	.699–1.492
	Stage	IIIa–b		1	
		I–II	.3958	.859	.605–1.220
	DFI	DFI ≤ 1		1	
		DFI > 1	.0044	.588	.408–.848
	Recurrence type	locoregional			
		distant	.6564	1.097	.730–1.647
		locoregional plus distant	.7154	1.157	.528–2.5356

[a]Model parameters (b_i) were converted to the relative risks by computing exp(b_i) where exp(a) = 2.7182[a].
[b]95% confidence interval for the relative was computed as [exp(b_{iL}), exp(b_{iH})] where b_{iL} = b_i-1.96 [estimated standard error(b_i)] and b_{iH} = b_i + 1.96 [estimated standard error(b_i)].
[c]Model 1 is calculated to estimate the risk of each factor for a disease-free interval.
[d]Model 2 is calculated to estimate the risk of each factor for the survival time calculated from the detection of recurrence.

of the operation. We created two kinetic models of recurrent lung cancer so that the DFI and postrecurrence survival would be 1 year (Fig. 3). In model 1, assuming a constant and uninterrupted tumor growth, there should have been a considerable amount of tumor cells even just after the operation. However, in model 2, if we assumed that surgery could reduce the tumor cell number more extensively, remnant tumor cells would need an accelerated growth to be detected within 1 year and to kill the patient within 2 years.

DISCUSSION

After a potentially curative resection for nonsmall cell lung cancer, the primary failure site was more likely to be distant metastases (70%) than either intrathoracic or regional lymph node recurrence (locoregional) (24%).

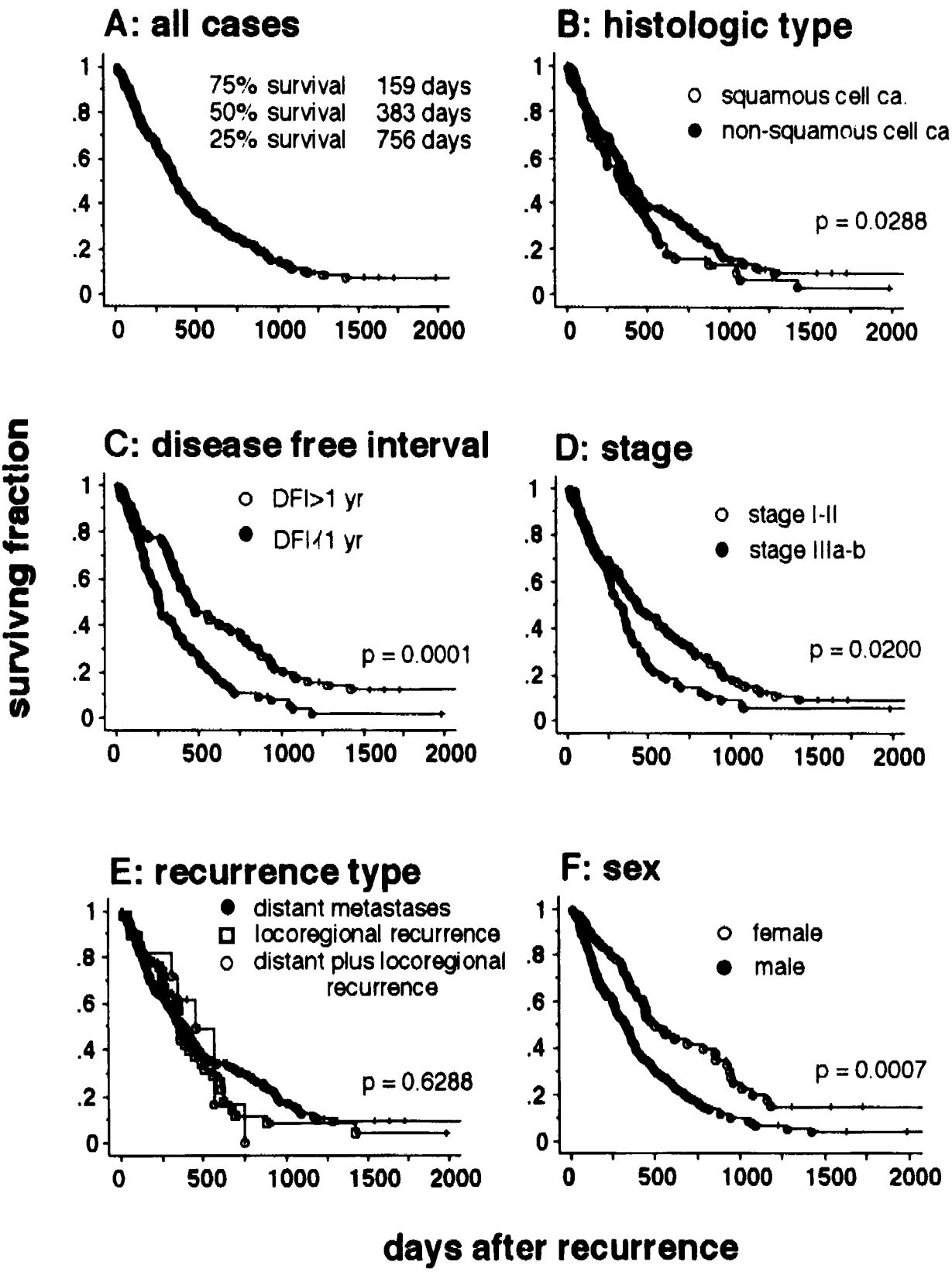

Fig. 2. Effects of various factors on the kinetics of survival after the detection of recurrence (post-recurrence survival).

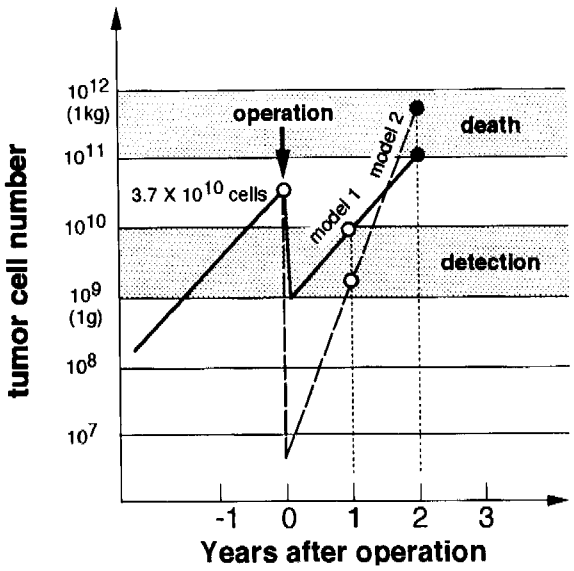

Fig. 3. Kinetic model of lung cancer recurrence. Tumor cells decreased in number after the operation (arrow). If the growth rate of the tumor remained unaltered before and after the operation, the tumor cell number should have been $\sim 10^9$ cells, which is just below the detection limit even after a curative operation, and capable of reaching 10^{11} cells and thus kill the patient within 2 years after the operation (model 1). However, if the number of the residual tumor cells was less (e.g., $<10^7$ cells, or 10 mg in model 2), then the tumor cells would have to have demonstrated an accelerated growth in order to reach 10^{11}–10^{12} cells within 2 years after the operation.

Among them, stage I disease was more likely to recur as distant metastases (71/90, 79%) than stage III disease (49/77, 64%) ($P = 0.029$). This confirms the finding of the previous report in which, for patients with N0 disease, the initial recurrence tended to demonstrate distant metastases, whereas in those with N1 disease, the initial recurrence was often more local [13]. However, two other studies reported opposite results, stating that the highest initial failure site in patients with stage I disease was in the ipsilateral hemithorax [14,15]. Nonsquamous cell carcinoma was likely to recur as a form of distant metastases (78%) compared with squamous cell carcinoma in which locoregional recurrence was found in 40%. A similar trend has also been reported by Pairolero et al. [4].

The median DFI was 395 days and the disease stage was the only significant variable contributing to a shortened DFI. This means that the occult or missed metastatic cells may be more in number in the advanced-stage patients than in the early-stage patients, if the growth rate is not dependent on the tumor stage. We also analyzed survival calculated from the day when recurrence was detected (postrecurrence survival). This information is particularly important when counseling a patient or a patient's family about prognosis of the disease. We found that the male gender and a short DFI were two independently significant predictors for a shortened survival by multivariate analysis, which thus confirmed the findings of our previous report [16]. Ichinose et al. [17] also reported that gender as well as the selection of adjuvant treatment is a predominant postrecurrent prognostic factor by multivariate analysis.

A potentially curative resection can be regarded as an operation that does not necessarily eradicate the tumor but just reduces the amount of tumor cells below the detection limit. The recurrence of the cancer is therefore just a manifestation of the metastatic disease that is present but occult and undetected at the time of surgery. To clarify how a tumor reappears after the operation, we created a kinetic model of recurrent lung cancer (Fig. 3). If a constant tumor growth was assumed, which was supported by the fact that DFI was a significant determinant of post recurrence survival, then a considerable number of tumor cells should have remained (Fig. 3, model 1). However, in model 2 (Fig. 3), the remnant tumor cells should have had an accelerated growth. Indeed, analysis of breast cancer indicates that the tumors grow faster before the time they were detected mammographically than after that time and that the tumor growth is modeled not in a form of exponential equation but of the logistic equation [9]. Probably these two models represent two extremes and in reality are intermingled. Model 1 (Fig. 3) indicates the need for a sensitive detection of micrometastatic remnant cancer cells. This possibly could be achieved by applying some of the recent advances in molecular genetics of cancer, since the detection of the micrometastatic tumor cells in such specimens as lymph node [18,19], or sputum [20], urine [21], or feces [22] have been successful. Model 1 (Fig. 3) also demonstrated the need to eliminate micrometastatic tumor cells following surgery by systemic therapy. However, previous studies in general failed to show any significant impact of the postoperative adjuvant chemo- and/or radiotherapy on either patient survival or the recurrence rate [2]. Model 2 agrees with the fact that removal of a primary tumor can result in a burst of growth in previously dormant micrometastases. Demicheli et al. [23] also showed that local recurrence following a mastectomy closely correlated with this concept. Holmgren et al. [24] reported that occult metastases probably escape the dormant state by increasing their angiogenic mechanism level by the disappearance of circulating angiogenesis inhibitors following the removal of a primary tumor. Furthermore, effect of tumor cell loss by exfoliation or apoptosis, which we did not take into account in our models, may not be negligible when considering actual tumor growth [25,26].

In conclusion, the concept of either a "curative" or "radical" resection is often merely optimism on the part of the surgeon when treating NSCLC. The sensitive and rapid detection of remnant occult micrometastases or the development of therapy to maintain tumor dormancy should thus be two of the objectives of future surgical oncology studies in order to improve the prognosis of this disease.

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